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6p24–22 Region and Major Psychoses in the Eastern Quebec Population

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Recent reports of a linkage trend in 6p24–22 for schizophrenia (SZ), in different samples, were tempered by the concurrent evidence of negative reports in other samples. In the studies showing positive results, different definitions of affection and a wide spectrum of diagnoses were used. Our objectives were not only to test for linkage at 6p24–22 in the Eastern Quebec population, but also to test whether this putative vulnerability locus was either selectively linked to schizophrenia (SZ), or to bipolar disorder (BP), or to both major psychoses. Parametric and nonparametric linkage analyses with 12 microsatellite markers in 6p24–p22 were performed on a sample of 18 large multigenerational pedigrees (N = 354) either affected by SZ, or by BP, or equally affected by both major psychoses (i.e., mixed pedigrees). Three affection definitions were usually tested in our program: one on schizophrenia (SZ), one on bipolar disorder (BP), and one that comprised SZ and BP under the hypothesis of a susceptibility locus common to both in major psychoses (common locus, CL). The *results* of parametric analyses did not support a major gene hypothesis. However, in one large mixed pedigree (≠151), we observed with the common locus phenotype (CL) lod scores of 2.49 and 2.15, respectively, at the D6S296 and D6S277 loci under a dominant model. Our data suggest the presence of a potential vulnerability locus at 6p24–22 that could be related to both schizophrenia and bipolar affective disorder. These results may be seen as congruent with former studies that used schizoaffective as well as schizophrenia diagnoses as entry criteria for the affected families, and used an affection definition that comprised affective psychoses as well as schizophrenia. Am. J. Med. Genet. 74:311–318, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: schizophrenia; bipolar disorder; linkage; heterogeneity; major psychoses

INTRODUCTION

Straub et al. [1995] recently reported a maximum lod score of 3.51 at the D6S296 locus when allowing for genetic heterogeneity and using a very broad definition of affection for schizophrenia. They estimated that 15–30% of their 265 Irish families showed linkage to this locus. In spite of considerable differences in sampling methods, ascertainment procedures, and affection definitions, three independent studies have also provided some evidence for a vulnerability locus in 6p24–22. Antonarakis et al. [1995], in a Baltimore sample, reported a Z_{max} of 1.17 at $\theta = 0.25$ with a recessive model at the D6S296 locus, using a narrow definition of affection (DSM-III-R schizophrenia and schizoaffective). Schwab et al. [1995] reported a Z_{max} of 2.2 near D6S274 in 54 German and Jewish families with at least 2 sibs affected by RDC schizophrenia (SZ) or schizoaffective (SZA) disorder. A third study done by Moises et al. [1995] reported a potential linkage at D6S274 in 65 families from different countries, using RDC or DSM-III-R SZ and SZA. A recent multicenter study also presented suggestive evidence of linkage on chromosome 6p [Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6, and 8, 1996].

While the consistency of these positive reports is encouraging, two studies reported negative results in

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6p24–22. Mowry et al. [1995], in 45 families from Australia and the United States, and Gurling et al. [1995], in 23 British and Icelandic pedigrees, observed negative findings with the same markers. In addition to methodological differences and other reasons mentioned above, populational differences and heterogeneity might explain the discrepant results. Given the numerous examples of linkage claims that failed replication [Baron, 1996; Sherrington et al., 1988; Egeland et al., 1987; McGuffin et al., 1990], the results accumulated so far have inspired caution [Baron, 1996].

Lander and Kruglyak [1995] concluded that the results obtained so far on 6p24–22 would enter the "significant linkage" category (statistical evidence expected to occur 0.05 times in a genome scan) and even the "confirmed linkage" category, without giving consideration to the fact that quite different phenotypic definitions were used. Others believe no firm conclusion can be drawn at this time [Baron, 1996].

While a linkage for psychotic disorders on chromosome 6p appears highly probable, the exact spectrum of major psychoses it applies to needs further investigation. Indeed, in all four studies showing positive results, it is noteworthy that, in terms of entry criteria, schizoaffective (SZA) as well as schizophrenia (SZ) diagnoses, or less stringent RDC criteria, were included. In family studies, schizoaffective disorder was found to be related to both schizophrenia and bipolar affective disorder [Kendler et al., 1995; Bertelsen and Gottesman, 1995]. In terms of affection definition, the study of Straub et al. [1995] used a very wide one comprising schizophrenia, schizoaffective, schizotypal, schizophreniform and delusional disorders, atypical psychosis, major depression and bipolar affective disorder with psychotic symptoms, and personality disorders (avoidant, paranoid, and schizoid). Moreover, in a recent genome-wide search in the Amish population, Ginns et al. [1996] reported, with bipolar disorder, a lod score of 2.34 at 6pter–p24 (the D6S7 locus) with congruent results with the sib pair analysis (P = .0003). D6S7 is located <15 cM telomeric to D6S296 [Donnis-Keller et al., 1987; Gyapay et al., 1994]. Altogether, these results raise the possibility that a linkage in the D6S296 area might be present in both schizophrenia and bipolar disorder.

The present study not only tested for linkage at 6p24–22 in our sample, but also looked at linkage with different disease categories (either schizophrenia or bipolar affective). We were in an ideal position to pose such a question by investigating large multigenerational pedigrees of the Eastern Quebec population affected by either schizophrenia (SZ) or bipolar affective disorder (BP), or affected almost equally by SZ and BP (mixed pedigrees) and assessed by the same ascertainment and blind methodology [Maziade et al., 1992].

PATIENTS AND METHODS

Sample and Diagnosis

The ascertainment procedure and its reliability have already been explained in detail elsewhere [Maziade et al., 1992, 1995a, 1995b]. In brief, all family members were administered, blind to proband diagnosis (SZ or BP), family relationships, and genotypes, a Consensus Best-Estimate Diagnosis according to DSM-III-R criteria and based on multiple sources of lifetime information (SCID interview, family history interviews, and medical records). All subjects were personally informed of the objectives and methods of the study, and each signed a consent form that was approved by the Ethics Committee of our University Center.

Our sample is in continuous progress through the extension of the already enrolled pedigrees and the enrollment of new pedigrees. The sample consisted of 8 multigenerational pedigrees densely affected by BP (no more than 15% of SZ spectrum disorders in the pedigree), 5 pedigrees affected by SZ (no more than 15% of BP spectrum disorder in the pedigree), and 5 mixed pedigrees affected almost equally (50 ± 5%) by SZ (and spectrum disorders) and BP (and spectrum disorders): a total of 354 genotyped and phenotyped individuals, of whom 98 were affected according to a narrow affection definition (CL1; see Statistical Analysis), and 122 according to a broad affection definition (CL2).

The sample characteristics were the following: mean age of onset for SZ (mean of 25.4 years, SD of 8.59 years) and for BP (types I and II) (mean of 28.8 years, SD of 10.3 years); mean current age for SZ, 43.8 years, and for BP, 56.4 years; mean duration of illness for SZ, 18.2 years, and for BP, 27.2 years; percentage of males for SZ, 48.0%, and for BP, 40.4%.

Statistical Analysis

In order to test for linkage, we used the lod score methods implemented in the FASTLINK programs [Lathrop and Lalouel, 1984; Cottingham et al., 1993; Schaffer et al., 1994]. First, we considered both affected and unaffected subjects in the analysis, and then the affecteds only. We predetermined six definitions of phenotype: 1) a narrow definition for SZ (SZ1) = schizophrenia alone; 2) a broad definition (SZ2) = SZ1 + schizophreniform + schizotypal; 3) a narrow definition for BP (BP1) = bipolar type I alone; 4) a broad definition for BP (BP2) = BP1 + bipolar type II + recurrent major depression; 5) a narrow definition of affection based on the hypothesis of a common locus for both SZ and BP (CL1), i.e., schizophrenia, bipolar type I, and schizoaffective; 6) and a broad definition (CL2) = CL1 + bipolar type II + recurrent major depression + schizophreniform + schizotypal + brief psychotic episode. We used two models of transmission, one dominant (frequency of disease allele, 0.01; cumulative penetrance, 0.70; 21% phenocopies) and one recessive (frequency of disease allele, 0.10; cumulative penetrance, 0.70; 10% phenocopies). Hence, 24 analyses were carried out for each marker. We also performed model-free analyses such as the Affected-Pedigree-Member (APM) method [Weeks and Lange, 1988; Schroeder et al., 1994] for testing identity-by-state (IBS) allele-sharing among affected family members and S.A.G.E. SIBPAL (Version 2.7) [Amos et al., 1989] for testing identity-by-descent (IBD) allele sharing among affected siblings.

We assessed the level of significance of our best lod score value empirically through simulation. The com-

puter program SIMULATE [Terwilliger and Ott, 1994] was used because it offers the advantage of rapidly generating markers unlinked to the disease locus. We generated 2,000 replicates of an unlinked marker made of four equally frequent alleles and calculated the frequency with which our lod score result was observed by chance alone. Such a large number of replicates was necessary since this frequency, representing the type I error, is expected to be very low (<1%) for a high lod score. Similarly, we assessed the probability of observing a given lod score in our sample if there were truly linkage between the disease and the marker. SLINK [Weeks et al., 1990] was used to generate a four-allele marker tightly linked to the disease ($\theta = 0$). As this probability is expected to be at least >10% in our sample, the generation of 200 replicates was sufficient to ensure the accuracy of the empirical estimate.

The two SZ phenotypic definitions were analyzed in the schizophrenia and mixed pedigrees (N = 210), and the two BP definitions were analyzed in the bipolar and mixed pedigrees (N = 237). The common locus definitions (CL1 and CL2) were analyzed in the total sample made of the SZ, the BP, and the mixed pedigrees (N = 354).

Genotyping Procedures

The MapPairs™ primers, used in this study, were purchased from Research Genetics (Huntsville, AL). PCR amplification of polymorphic alleles was done essentially according to the manufacturer's instructions, in the presence of 100 ng of high molecular weight genomic DNA isolated from immortalized B-lymphocytes, [^{32}P]-5′-end-labeled primers, and *Taq* DNA polymerase (GIBCO-BRL, Burlington, Ontario, Canada). Samples were denatured at 94°C for 2 min and submitted to 24 amplification cycles of 94°C for 30 sec, 55°C for 30 sec, and 72°C for 30 sec. The electrophoresis of PCR-amplified samples was conducted on polyacrylamide-urea denaturing sequencing gels, in parallel with samples from normal controls for allele identification and a pUC19 sequencing ladder for allele size determination. The autoradiograms were read by two investigators, independently and blind to the phenotypes.

RESULTS

First, we constructed a map of intermarker distances (Fig. 1) and found it to be very similar to a previously published map [Gyapay et al., 1994]. Table I summarizes the main positive results with two tightly linked markers, D6S277 and D6S296. The highest lod score values of 2.15 ($\theta = .00$) and 2.49 ($\theta = .00$) were respectively observed at these two loci in one pedigree (#151), using the broad common locus phenotype (CL2) under the dominant model with the analysis considering both affecteds and unaffecteds. Such high lod scores were not observed in the other families or in the total sample. Figure 1 summarizes the results in pedigree 151 obtained with the analysis of the affecteds and unaffecteds. For the BP2 and CL2 phenotypes, lod scores >1 were found for almost all markers between F13A1 and D6S259. These trends were not observed with the schizophrenia phenotypes. Figure 2 illustrates the structure of pedigree 151 that, over three generations, contains three schizophrenic, three bipolar, one major depressive, and two dysthymic subjects.

Three-point linkage analyses were performed in pedigree 151 using the CL2 phenotype, under the dominant model and with all combinations of 2 of the 4 following markers: D6S277, D6S296, D6S309, and D6S470. The highest three-point lod score of 2.14 was obtained with D6S277 and D6S296. No recombination was observed between the disease and either of these two markers or between markers. The three-point lod score value of 2.14 reflects the greater informativeness of D6S277 over that of D6S296 for generation 2. We performed a sensitivity analysis in pedigree 151, using the most informative marker (D6S277). One at a time, each affected individual became unknown. This yielded 7 lod scores ranging from 1.24–3.00. Hence, the original lod score of 2.15 was not highly dependent on any one particular individual. We verified the dependency of the result in pedigree 151 on the phenocopy rate specified in our transmission model. The penetrance for homozygous noncarriers was set to zero and the data were reanalyzed to obtain a lod score of 1.83, a value not so different from the original ones. The significance of a lod score of 2.15 was assessed through the simulation of 2,000 replicates of the segregation of an unlinked marker in pedigree 151. The probability of observing a value of 2.15 or greater was estimated to be .0025. The simulation of 200 replicates of a linked marker ($\theta = 0.00$) estimated at 0.33 the probability of observing a value of 2.15 or greater if the marker were truly linked to the disease.

In the whole sample, two-point APM results were nonsignificant for all markers and all phenotypes tested. Similarly, none of the multipoint APM results were significant. However, we observed significant two-point IBS allele-sharing in pedigree 151 for D6S277 under BP2, CL1, and CL2 (empirical *P*-values < 0.004 for 2 weighting functions), but not for D6S296.

Congruent with the linkage results at D6S296 and D6S277 in the total sample, the investigation of IBD allele-sharing at these loci showed no significant results in the whole sample. IBD allele-sharing was observed for D6S259, D6S89, D6S260, and D6S274 for the schizophrenia phenotype (estimated proportions of allele-sharing of .55–.66, $P < .05$ $P < .01$), but most of this evidence came from one family (#250) in which 5 sibs affected by SZ provided 10 pairs out of the 86 (for CL1) and 104 (for CL2) sib pairs. Eighty percent of allele-sharing was observed within this sibship alone.

In addition to our usual affection definitions, we analyzed in our sample all markers with the affection definition (D1–D8) and transmission model (Pen model) of Straub et al. [1995], which yielded positive results in their two-point linkage analyses. In pedigree 151, we obtained a Z_{max} of 1.11 ($\theta = .00$) with D6S296. When we further analyzed the data according to our own predetermined dominant model, the highest result was a lod score of 1.83 ($\theta = .00$) in pedigree 151 at the D6S296 locus (see Fig. 1). Two-point APM results were nonsignificant.

TABLE I. Maximum Lod Scores and Recombination Fraction Estimates With Broad Phenotype Definitions Under a Dominant and a Recessive Model*

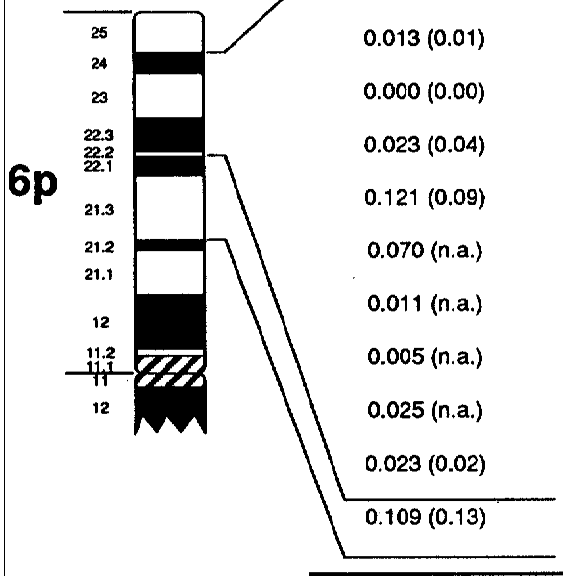
Pedigree number	Phenotype definition: Broad SZ phenotype definition, D6S296, DOM	Broad SZ phenotype definition, D6S296, REC	Broad SZ phenotype definition, D6S277, DOM	Broad SZ phenotype definition, D6S277, REC	Broad BP phenotype definition, D6S296, DOM	Broad BP phenotype definition, D6S296, REC	Broad BP phenotype definition, D6S277, DOM	Broad BP phenotype definition, D6S277, REC
211A s	0.63 (0.00)	0.74 (0.00)	0.64 (0.00)	0.74 (0.00)	NI	NI	NI	NI
220 s	0.60 (0.00)	0.13 (0.15)	0.60 (0.00)	0.13 (0.15)	NI	NI	NI	NI
228 s	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	NI	NI	NI	NI
250 s	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	NI	NI	NI	NI
255 s	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	NI	NI	NI	NI
101 m	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.09 (0.35)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.01 (0.35)
103 m	0.00 (0.50)	0.02 (0.35)	0.00 (0.50)	0.01 (0.35)	0.00 (0.50)	0.00 (0.50	0.00 (0.50	0.00 (0.50)
151 m	0.27 (0.00)	0.86 (0.00)	0.14 (0.00)	0.62 (0.00)	**1.68 (0.00)**	**1.85 (0.00)**	**1.45 (0.00)**	**1.84 (0.00)**
218 m	0.08 (0.10)	0.00 (0.50)	0.06 (0.15)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)
230 m	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)
105 b	NI	NI	NI	NI	0.00 (0.50)	0.02 (0.25)	0.00 (0.50)	0.00 (0.50)
110 b	NI	NI	NI	NI	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)
111 b	NI	NI	NI	NI	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)
125 b	NI	NI	NI	NI	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)
125A b	NI	NI	NI	NI	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)
182 b	NI	NI	NI	NI	0.04 (0.00)	0.00 (0.50)	0.06 (0.35)	0.00 (0.50)
211 b	NI	NI	NI	NI	0.25 (0.25)	0.55 (0.15)	0.43 (0.20)	0.55 (0.15)
212 b	NI	NI	NI	NI	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.02 (0.25)
Total	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.01 (0.35)	0.00 (0.50)	0.42 (0.30)	0.20 (0.35)	0.41 (0.25)

Pedigree number	Phenotype definition: Broad common locus phenotype definition, D6S296, DOM	Broad common locus phenotype definition, D6S296, REC	Broad common locus phenotype definition, D6S277, DOM	Broad common locus phenotype definition, D6S277, REC
211A s	0.63 (0.00)	0.74 (0.00)	0.64 (0.00)	0.74 (0.00)
220 s	0.60 (0.00)	0.13 (0.15)	0.60 (0.00)	0.13 (0.15)
228 s	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)
250 s	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)
255 s	0.10 (.25)	0.00 (0.50)	0.16 (.25)	0.21 (0.15)
101 m	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)
103 m	0.00 (0.50)	0.02 (0.35)	0.00 (0.50)	0.08 (0.25)
151 m	**2.49 (0.00)**	**1.69 (0.00)**	**2.15 (0.00)**	**1.52 (0.00)**
218 m	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)
230 m	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)
105 b	0.02 (0.25)	0.00 (0.50)	0.09 (0.20)	0.00 (0.50)
110 b	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)
111 b	0.00 (0.50)	0.04 (0.25)	0.00 (0.50)	0.20 (0.15)
125 b	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)
125A b	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)
182 b	0.00 (0.50)	0.00 (0.50)	0.01 (0.35)	0.00 (0.50)
211 b	0.00 (0.50)	0.01 (0.35)	0.36 (0.20)	0.00 (0.50)
212 b	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.01 (0.35)
Total	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.18 (0.35)

*s, schizophrenia pedigree; m, mixed pedigree; b, bipolar pedigree. $Z_{max} > 1.0$ are in bold. NI indicates that the pedigree was not informative, for it did not contain any affected individuals under the specified phenotype definition. DOM: dominant; REC: recessive.

DISCUSSION

Our results suggest no major gene effect on chromosome 6p24–22 in the Eastern Quebec population. However, in the context of four recent reports of modest but significant linkage trends at 6p24–22 in samples of families from Ireland, United States, and Germany [Straub et al., 1995; Antonarakis et al., 1995; Schwab et al., 1995; Moises et al., 1995], our observation of high lod scores in one large pedigree is noteworthy. This result is especially congruent with the study of Straub et al. [1995] in three respects. First, the statistical effect we observed was modest, and this has been interpreted as a possible reflection of complex or oligogenic inheritance [Straub et al., 1995; Cloninger, 1994; Risch and Botstein, 1996; Maziade and Raymond, 1995]. These findings might also be due to uncertainty about the most valid phenotype definition [Tsuang, 1994; Cloninger, 1994; Baron, 1996]. Second, only one large pedigree of our sample showed a linkage trend, suggesting heterogeneity in our population. Such heterogeneity was also observed in the Irish population [Straub et al., 1995] that showed linkage in 15–20% of the



Intermarker recombination fraction estimate	Marker/ locus	SZ2		BP2		CL2		D1-D8*	
		Dominant Zmax (θ)	Recessive Zmax (θ)	Dominant Zmax (θ)	Recessive Zmax (θ)	Dominant Zmax (θ)	Recessive Zmax (θ)	Dominant Zmax (θ)	Recessive Zmax (θ)
	F13A1	0.03 (0.00)	0.09 (0.00)	**1.07 (0.00)**	**1.87 (0.00)**	**1.15 (0.00)**	**1.31 (0.00)**	0.49 (0.00)	0.12 (0.20)
0.019 (n.a.)	D6S309	0.00 (0.50)	0.00 (0.50)	**2.07 (0.00)**	**1.33 (0.00)**	0.52 (0.05)	**1.59 (0.00)**	0.00 (0.50)	**1.06 (0.00)**
0.013 (0.01)	D6S296	0.27 (0.00)	0.86 (0.00)	**1.68 (0.00)**	**1.85 (0.00)**	**2.49 (0.00)**	**1.69 (0.00)**	**1.83 (0.00)**	0.27 (0.10)
0.000 (0.00)	D6S277	0.14 (0.00)	0.62 (0.00)	**1.45 (0.00)**	**1.84 (0.00)**	**2.15 (0.00)**	**1.52 (0.00)**	**1.49 (0.00)**	0.38 (0.15)
0.023 (0.04)	D6S470	0.03 (0.20)	0.17 (0.10)	**1.01 (0.00)**	0.87 (0.00)	**1.38 (0.00)**	0.80 (0.00)	0.80 (0.05)	0.58 (0.00)
0.121 (0.09)	D6S259	0.00 (0.50)	0.00 (0.50)	**1.03 (0.00)**	0.44 (0.10)	**1.41 (0.00)**	0.97 (0.00)	0.75 (0.00)	0.30 (0.15)
0.070 (n.a.)	D6S89	0.00 (0.50)	0.02 (0.35)	0.00 (0.50)	0.00 (0.50)	0.40 (0.00)	0.12 (0.10)	0.38 (0.00)	0.96 (0.00)
0.011 (n.a.)	D6S260	0.00 (0.50)	0.02 (0.35)	0.01 (0.20)	0.17 (0.00)	0.39 (0.05)	0.24 (0.00)	0.31 (0.00)	0.34 (0.00)
0.005 (n.a.)	D6S334	0.04 (0.25)	0.21 (0.10)	0.92 (0.00)	0.63 (0.10)	**1.46 (0.00)**	0.45 (0.05)	0.85 (0.05)	0.51 (0.10)
0.025 (n.a.)	D6S274	0.00 (0.50)	0.01 (0.35)	0.08 (0.20)	0.02 (0.25)	0.14 (0.15)	0.23 (0.15)	0.08 (0.35)	0.19 (0.15)
0.023 (0.02)	D6S285	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.02 (0.25)	0.00 (0.50)	0.05 (0.20)	0.00 (0.50)	0.02 (0.20)
0.109 (0.13)	D6S273	0.45 (0.00)	0.09 (0.00)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)	0.00 (0.50)

Fig. 1. Maximum lod scores (Z_{max}) from two-point linkage analyses at 6p24–p22 in pedigree 151. *D1–D8 refers to phenotype definition of Straub et al. [1995]. Intermarker distances from Gyapay et al. [1994] are in parentheses. Intermarker recombination fraction estimates are results from two-point lod scores calculated with ILINK in our sample of 18 families. n.a., not available. Dominant transmission model (frequency of disease allele, 0.01; cumulative penetrances, 0.70; phenocopies, 21%); recessive (frequency of disease alleles, 0.10; cumulative penetrance, 0.70; phenocopies, 10%). Lod scores >1.0 are in bold.

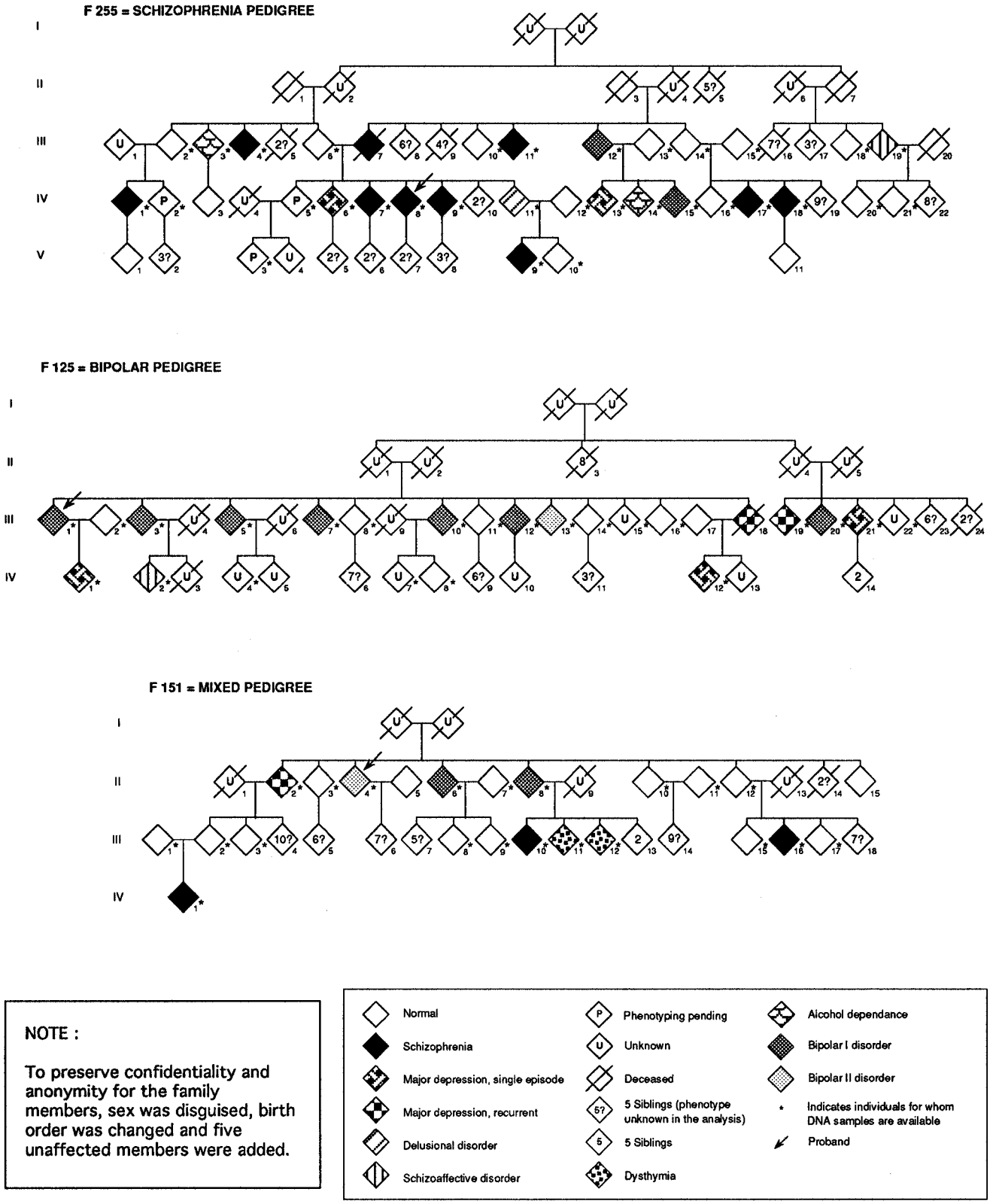


Fig. 2. Examples of a schizophrenia pedigree, a bipolar pedigree, and a mixed pedigree.

families under study. Third, the marker loci showing the highest lod scores in our study (D6S296 and D6S277) are also congruent with the findings of Straub et al. [1995].

As regards our second research question about the comparative analyses of the schizophrenia spectrum phenotypes and the bipolar spectrum phenotypes, our results in one mixed pedigree suggest the possibility that the potential vulnerability gene located at 6p24–22 would not be specific to schizophrenia but could also be related to bipolar affective disorder. We observed indeed that our predetermined broad common phenotypic definition (CL2: schizophrenia, schizoaffective, schizophreniform, brief psychosis, bipolar I and II disorder, and major depression recurrent) yielded the highest lod scores in one large pedigree affected by both schizophrenia and bipolar disorder. The narrow and broad schizophrenia definitions (SZ1 and SZ2) showed no linkage trend in the parametric analyses. The present modest linkage trend could also be compatible with the slight but significant trend observed at 6pter–p24 for bipolar disorder in the Amish population [Ginns et al., 1996].

Our observation that the 6p24–22 may be linked in our sample to both schizophrenia and bipolar spectrum disorders is not incongruent with the findings of Straub et al. [1995], who interpreted their results as a linkage trend with schizophrenia. First, in the latter study, the affection definition that yielded a positive linkage comprised affective psychoses such as bipolar disorder and major depression in addition to schizophrenia and schizoaffective disorder. In that respect, it is interesting to note that when we used the affection definition (D1–D8) of Straub et al. [1995] in our sample, this also yielded a positive trend (lod score of 1.83) in pedigree 151 but not in the others. Second, in terms of entry criteria, Straub et al. [1995] used schizoaffective disorder or schizophrenia for the two affected probands of their multiplex families. Family studies [Kendler et al., 1995; Bertelsen and Gottesman, 1995] have shown schizoaffective disorder to be in the familial spectrum of both schizophrenia and bipolar disorder, and probably bearing liability to both disorders [Kendler et al., 1995]. Moreover, the reliability of the schizoaffective diagnosis is low in several studies [Maziade et al., 1992; Hostetter et al., 1983; Leboyer et al., 1991; McGorry et al., 1990; Fennig et al., 1994]. Incidentally, Antonarakis et al. [1995], Mowry et al. [1995], and Moises et al. [1995] also included schizoaffective disorder in the affection definition that yielded modest positive linkage trends at 6p24–22. What is not known is the extent to which the inclusion of schizoaffective disorder as an entry criteria for small schizophrenia multiplex families might introduce an affective etiological component in the sampling of such small families. Such families can, in fact, be affected by two schizophrenic, one schizophrenic and one schizoaffective, or two schizoaffective patients. Several studies have already suggested [Cloninger, 1994; Maziade et al., 1992, 1995a] including, whenever possible, only schizophrenia at the first hierarchical diagnostic level for linkage studies of schizophrenia.

More studies in large samples of schizophrenia and bipolar families will be needed to clarify these issues. More attention to the differences among the studies in terms of the definitions of phenotype [Cloninger, 1994] will also be helpful in the interpretation of congruencies and incongruencies among these studies.

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